

PATENT SPECIFICATION

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The Inventors of this invention in the sense of being the actual devisers thereof within the meaning of Section 16 of the Patents Act 1949 are:— WERNER REIF and HORST POMMER,, citizens of the Federal Republic of Germany, residing, respectively, at 2 Ungsteiner Strasse, Ludwigshafen/Rhein; and 174 Lisztstrasse, Ludwigshafen/Rhein; Federal Republic of Germany.

COMPLETE SPECIFICATION

Production of Compounds containing an olefinic double bond

We, BADISCHE ANILIN- & SODA-FABRIK AKTIENGESELLSCHAFT, a German Joint Stock Company, of Ludwigshafen/Rhein, Federal Republic of Germany, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following Statement:—

This invention relates to the production of compounds containing an olefinic double bond by the reaction of phosphorus ylids with carbonyl compounds.

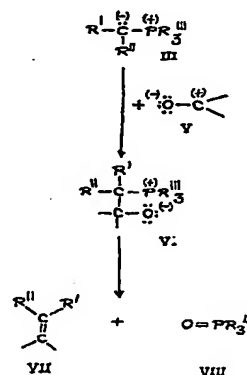
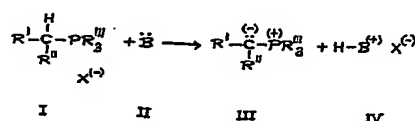
Phosphorus ylids are compounds in which a carbanion is covalently bonded to a phosphorus atom having a positive charge:



Reactions of phosphorus ylids have for some years been firmly established tools of preparative organic chemistry and are beginning to find application in commercial operations.

The Wittig reaction of phosphorus ylids to produce olefins has achieved special importance. In this reaction, a base II (see equation below) acting as a proton acceptor is allowed to act on a phosphonium compound of the general formula I where R' and R'' are hydrogen, saturated or unsaturated cycloaliphatic, araliphatic or aromatic radicals that may bear further substituents, R''' is an alkyl, cycloalkyl or aryl radical and X⁻ is the equivalent of an anion, the corresponding ylid III and a salt IV being obtained. The strongly nucleophilic carbanion contained in the ylid can

then react with a carbonyl compound in the polarized state V, in which the carbonyl carbon is strongly electrophilic, affording the betaine VI. The latter eliminates the corresponding tertiary phosphine oxide VIII and is converted into the olefin VII with the formation of a C=C double bond.



In carrying out this outstanding process, particularly on a commercial scale, optimum results will not be achieved unless a number of critical points are carefully observed. For ex-

ample, the proton acceptor II may well react with the unsaturated carbonyl compound V. The salt IV may be precipitated in crystalline or viscous form and interfere with or prevent efficient mixing of the reactants. In the production of sensitive olefins VII, which may contain other functional groups in addition to one or more double bonds, the proton acceptor II and/or the ylid III may react with the reaction product in an undesirable manner. The formation of the ylids and their further reaction are frequently strongly exothermic so that local overheating may occur. Unless these and other phenomena are carefully observed, especially when several of them occur simultaneously, considerable losses in yield and disturbances in operation may result. Although the difficulties may occasionally be overcome, it has been desirable to find ways to reduce the amount of supervision and the number of precautionary measures in continuous operation, to avoid operational disturbances and achieve better results.

It has been found that, unexpectedly, the production of a compound containing an olefinic double bond by a process involving the reaction of an ylid with a carbonyl compound can be carried out reliably and with very small losses in yield by

- (a) continuously contacting the ylid and the carbonyl compound in a substantially constant molar ratio and continuously removing the reaction mixture containing the compound containing an olefinic double bond from the place where contacting is effected, or by
- (b) continuously contacting a phosphonium salt which yields the phosphorus ylid with a proton acceptor and the carbonyl compound in a substantially constant molar ratio and continuously removing the reaction mixture containing the compound containing an olefinic double bond from the place where contacting is effected.

The preferred ratio of phosphonium salt to proton acceptor is 1:1 to 1:2 equivalents and the preferred ratio of ylid to electrophilic partner is 1:1 equivalent.

Various types of apparatus and equipment can be used to carry out the process according to the present invention, e.g. nozzles, stirred reactors and circular tube systems. According to one embodiment of the process, the solution of one of the reactants is passed through a tube and the solution of the other reactant is introduced through a nozzle arranged inside the same tube. The diameter of the tube, the shape of the nozzle and the rate of flow can be correlated so that mixing occurs and the two solutions are thoroughly mixed without any mechanical measures. The mixing effect may however be increased by providing stationary mixing means or stirring means.

In this process the solution of the ylid may be passed either through the tube or through the nozzle. The same is true of the solution of the carbonyl compound. It is also possible to run the mixture of phosphonium salt and carbonyl compound through one member and the proton acceptor through the other. Another modification consists in arranging two nozzles one after the other, allowing the ylid to form in the vicinity of the first nozzle and contacting the ylid with the carbonyl compound in the vicinity of the second nozzle.

Instead of providing a nozzle inside a tube, two nozzles or two thin tubes may be made to project into a thicker tube on opposite sides or adjacent to each other, the solutions containing the reactants being supplied through the thin tubes. If desired, additional solvent may be passed through the thicker tube.

According to another embodiment the reactants are contacted in a stirred reactor instead of through nozzles. In this case the three reactants are expediently passed through a comparatively small mixing vessel in which turbulent flow is produced by a suitable stirrer and rigid mixing elements. In this embodiment, too, it may be advantageous to first combine components I and II or I and IV in a mixer and then add the carbonyl compound V or proton acceptor II in a second mixer.

Another possibility is to use a circular tube system, especially when the reaction is strongly exothermic. In this case, as in the case of the tube described above, the three reactants are introduced simultaneously into the recirculating reaction mixture.

The reaction components may be combined as such instead of as solutions provided they are liquid under the reaction conditions, although solutions offer the advantage of being easier to meter and to mix and of the heat being more efficiently removed.

The heat of reaction may if necessary be removed adiabatically by cooling the solutions of the reaction components or the liquid reaction components themselves before contacting them.

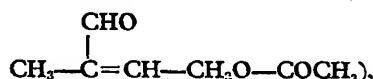
The heat of reaction may also be removed by evaporative cooling, by external cooling or by introducing an additional cooled solvent. For evaporative cooling, a solvent, an auxiliary medium or a reactant which boils under the conditions of the process is used. On the other hand, complete reaction of the reaction components may be promoted by heating the reaction mixture at a suitable distance from the place where the reaction components are combined. Smaller residence zones or vessels, if any, may then be used.

Among the phosphonium compounds I (which may be prepared continuously from the compounds $P(R''')$, and $(R'')(R'')CHX$, those are preferred which are derived from triphenylphosphine and chlorides, bromides, iodides or the corresponding hydroxyl deriv-

atives of saturated or unsaturated hydrocarbons having from 1 to 30 carbon atoms.

Suitable proton acceptors for the production of the ylids are all compounds usually employed for the preparation of ylids by conventional techniques. Examples are organo-metallic compounds, such as phenyllithium or sodium acetylide, Grignard compounds, organic bases, such as alcoholates or amines, inorganic bases, such as alkali metal or alkaline earth metal hydroxides, or basic ion exchange resins. In the last-mentioned case the ylid is prepared by treating the solution of the onium compound with a basic ion exchange resin before being fed to the mixing equipment.

Carbonyl compounds which may be used include, in particular, ketones and aldehydes and above all those which in addition to the C=O function have one or more conjugated double bonds. They may however also contain triple bonds in the molecule. Aldehydes and ketones having saturated or, preferably, unsaturated aliphatic or cycloaliphatic-aliphatic residues with a total of 2 to 30 carbon atoms are particularly important industrially. Aldehydes and ketones of the said type, which are suitable for the synthesis of physiologically active compounds of the polyene series, are for example 2 - methyl - 2 - butenol, 3 - formyl - crotyl acetate (i.e.



ethyl 3 - formyl - crotonate (i.e.



β -ionone, citral, 2 - methyl - hept - 2 - en - one, β -ionylidene acetaldehyde and vitamin-A aldehyde.

Suitable solvents or diluents are especially those that do not react with the ylids or other components of the reaction mixture under the temperature conditions chosen. The large number of suitable solvents includes aliphatic and aromatic hydrocarbons, alcohols, carboxylic esters, ethers, cyclic ethers, halohydrocarbons, carboxylic amides, nitriles and even water. A particular solvent or solvent mixture may have to be tested to see that it does not react with either the ylid or the compound to be reacted with the ylid.

The invention will now be further illustrated with reference to an advantageous embodiment of the process.

A 1M solution of a phosphonium compound (I) in methanol is continuously contacted in a mixing nozzle with an approximately equimolar amount of a carbonyl compound (V) and the mixture is cooled to -25 to -30°C in a cooling zone. A 1M solution of sodium

methylate in methanol, which has also been cooled to -25 to -30°C , is then injected and the three components thus brought to reaction. The reaction mixture heats up immediately to 0 to 5°C . The reaction proceeds to completion in a zone with an average residence period of 10 minutes, the mixture heating up to 20 to 25°C . The reaction mixture may be worked up in conventional manner by using dilute aqueous acid and extracting with a hydrophilic solvent.

Generally speaking, the process according to this invention is expediently carried out at temperatures between -30 and $+60^\circ\text{C}$ using residence periods between 10 seconds and 30 minutes. The reaction is then stopped by acidification as in the case of batchwise operation.

Although the process according to the present invention is suited to all reactions of ylids, its advantages are particularly evident when the ylids III to be reacted have low stability or cannot be isolated in substance or can be isolated only with difficulty. This is the case whenever the ylid function is not stabilized by other groups present in the molecule, particularly groups which are capable of resonance stabilization.

The advantages of this invention can be summarized by stating that the desired reaction is favored, while undesired side reactions are suppressed. The products are obtained in excellent purity and high yield. Moreover, the process of this invention can be carried out in commercial equipment of practically any size. The said advantages are particularly evident when the substances to be reacted with the ylid or the products themselves are highly sensitive compounds. Thus, the new process lends itself particularly to the synthesis of vitamins, hormones, carotenoids and polyene compounds.

WHAT WE CLAIM IS:—

1. A process for production of a compound containing an olefinic double bond by reacting a phosphorus ylid with a carbonyl compound wherein the phosphorus ylid is continuously contacted with the said carbonyl compound in a substantially constant molar ratio and the reaction mixture containing the compound an olefinic double bond is continuously removed from the place where contacting is effected.

2. A process for production of a compound containing an olefinic double bond by reacting a phosphorus ylid with a carbonyl compound wherein a phosphonium salt which yields the phosphorus ylid is continuously contacted with a proton acceptor and a carbonyl compound in a substantially constant molar ratio and the reaction mixture containing the compound containing an olefinic double bond is continuously removed from the place where contacting is effected.

3. A process as claimed in claim 1 or 2 wherein at least one of the reactants is cooled

before being supplied in liquid or dissolved form to the zone where contacting is carried out.

5 4. A process as claimed in any of claims 1 to 3 wherein heat of reaction is removed by evaporative cooling.

10 5. A process as claimed in any of claims 1 to 4, wherein the reactants are contacted in a mixing nozzle, a stirred reactor or a circular tube system.

6. A process as claimed in claim 1 or 2 sub-

stantially as hereinbefore described and exemplified.

7. A compound containing an olefinic double bond when produced by a process claimed in 15 any of claims 1 to 6.

J. Y. & G. W. JOHNSON,
Furnival House,
14—18 High Holborn,
London, W.C.1,
Chartered Patent Agents,
Agents for the Applicants.

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